Aldol Addition of a Lithium Ketone Enolate with Persubstituted Double Bond – a Reversal of the Usual Stereochemical Course**

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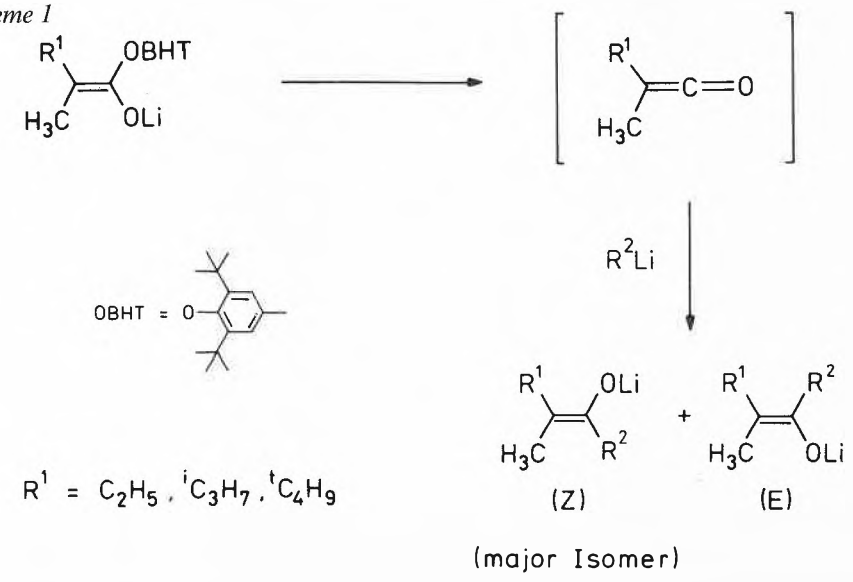
Abstract: The lithium (*Z*)-3,4,4-trimethyl-1-phenyl-2-penten-2-olate generated in situ from *tert*-butyl(methyl)ketene and benzyllithium adds to benzaldehyde with relative topicity *lk*, as shown by X-ray crystal structure analysis of the aldol adduct. Possible reasons for this unusual steric course are discussed.

Recently we reported the regio- and stereoselective formation of lithium ketone enolates with tetrasubstituted double bonds[1]. Trapping of unsymmetrical ketenes, generated in situ from BHT ester enolates (BHT = 2,6-di-*tert*-butyl-4-methylphenol, «*b*utylated *h*ydroxy*t*oluene»), was shown by NMR spectroscopy of the corresponding silyl enol ethers to occur from the less hindered side, thus providing preferentially (*Z*)-enolates (see Scheme 1).

Scheme 1



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Additions of these enolates to aldehydes gave the aldol adducts with diastereoselectivities of up to 99%. In analogy to the less substituted cases (Zimmermann-Traxler model) we assumed, without proof, that the combination of the two trigonal centers proceeded with relative topicity *ul*[2]. We have now realized an X-ray crystal structure analysis of the aldol **3** obtained from the enolate **1** and benzaldehyde (**2**). Much to our surprise, the product turned out to possess the relative configuration *l*, as can be seen from the ORTEP plot in Fig. 1.

Steric hindrance between the phenyl ring of the benzaldehyde and the *tert*-butyl group of the enolate is obviously too severe

if the two trigonal centers approach in the conventional way (**B**). The *quasi* 1,3-diaxial disposition of the phenyl and benzyl groups in approach **A** causes less hindrance (compare the diminished selectivities of additions of aldehyde enolates[3]). Furthermore, the favourable arrangement of the smaller substituent (CH_3) of the enolate *antiperiplanar* to the C=O double bond – causing less steric hindrance to the Bürgi-Dunitz trajectory[4] – is realized in **A** (cf. **C**). Other approaches resembling cyclohexane boat[3,5] or twist forms[6] and so-called open transition states[3] leading to the observed product **3** all have the phenyl and the *tert*-butyl groups next to each other (see Scheme 2).

X-ray analysis of **3**:

Single crystals of **3** (*m.p.* 92.8–93.2 °C) were obtained by recrystallization from pentane/ether at −30 °C. **3** forms crystals of the rhombic space group $R\bar{3}$, $a = 15.54$ Å, $\alpha = 110.51°$, $V = 2772.2$ Å^3, $Z = 6$, $\rho_x = 1.12$ g cm^{-3}, $C_{21}H_{26}O_2$. 2123 independent reflexions of a crystal (1202 with $I > 3\sigma(I)$) were measured with an Enraf Nonius CAD-4 diffractometer at room temperature out to $\sin\theta/\lambda = 0.527$ Å^{-1} ($Mo_{K\alpha}$ radiation, $\lambda = 0.7107$ Å). The structure was solved by direct methods[7] and refined by full-matrix least-squares analysis[8]. The positions of all H-atoms except the H(O) were calculated. The refinement (C- and O-atoms anisotropically, H-atoms riding on C-atoms with free isotropic displacement parameters) with unit weight converged to $R = 0.105$[9].

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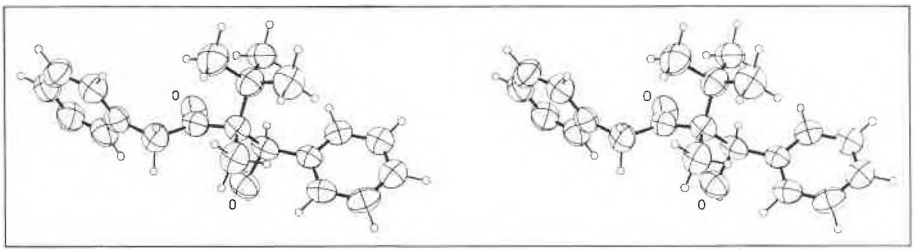
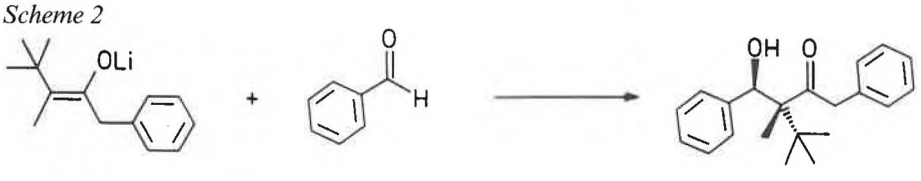
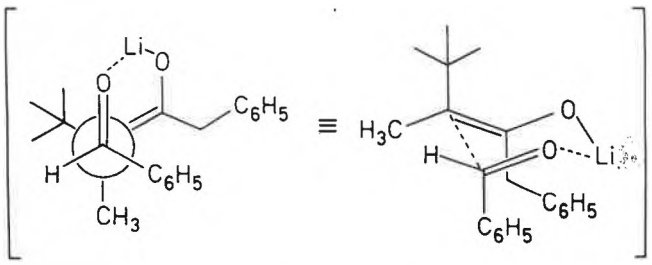


Fig. 1. ORTEP stereoview of the aldol **3**. *Ellipsoids are drawn at the 50% probability level.*

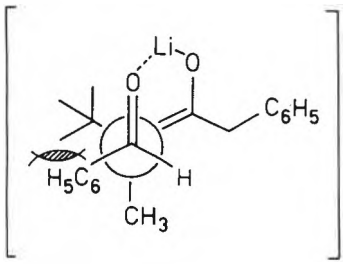
Scheme 2



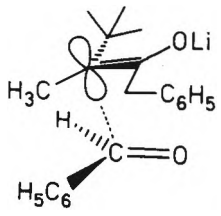
1 **2** **3** (ℓ)



A (ℓk)



B (uℓ)



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[1] R. Häner, T. Laube, D. Seebach, *J. Am. Chem. Soc. 107* (1985) 5396; D. Seebach, R. Amstutz, T. Laube, W.B. Schweizer, J.D. Dunitz, *ibid. 107* (1985) 5403.

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[3] For a discussion and leading references see: C.H. Heathcock, in J.D. Morrison (Ed.): *Asymmetric Synthesis*, Vol. *2*, Academic Press, New York (1983), chapter 2.

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[5] a) I. Kuwajima, E. Nakamura, *Acc. Chem. Res. 18* (1985) 181; b) E. Nakamura, I. Kuwajima, *Tetrahedron Lett. 24* (1983) 3343.

[6] Cf. the discussion by *Nakamura* and *Kuwajima*[5] who found a reversal of the steric course in the $TiCl_4$-mediated aldol addition to benzaldehyde when going from cyclohexenyl to 2-methyl-cyclohexenyl trimethylsilylether. They explain this by a change of the transition state from a tilt boat to the conventional chair.

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[8] G.M. Sheldrick, *SHELX 76. Program for Crystal Structure Determination*, University Chemical Laboratory, Cambridge, England (1976); J.P. Stewart, G.J. Kruger, H.L. Ammon, C. Dickenson, S.R. Hall, in «The X-ray System 1972», *Tech. Rep. TR-192*, Computer Science Center, University of Maryland, College Park MD, USA.

[9] Atomic coordinates are deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.